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(54) Title: PHARMACEUTICAL COMPOSITION WITH A CONTENT OF CALCIUM OR MIXTURE OF CALCIUM AND VITAMIN D OR MIXTURE OF CALCIUM AND MAGNESIUM IN A NEW FORMULATION

(57) Abstract: The pharmaceutical composition with the content of calcium or mixture of calcium and vitamin D or mixture of calcium and magnesium and adjuvants in the form of instant powder which after adding a liquid forms after a short mixing a pudding-like gelled suspension tolerated during use by patients.

Pharmaceutical composition with a content of calcium or mixture of calcium and vitamin D or mixture of calcium and magnesium in a new formulation

Technical Field

The invention from the pharmaceutical field relates to a therapeutical preparation with the content of calcium or mixture of calcium and vitamin D or mixture of calcium and magnesium for a long-term peroral use for prevention and treatment of primary and secondary osteoporosis and for correction of hyperphosphataemia in patients in advanced stages of renal insufficiency.

Background Art

It is well known, that some patients suffer from a deficit of calcium despite of its sufficient intake in diet. The reason is the impaired resorption in intestine cells.

The formulations with a content of calcium, known in the art, have used as a source of calcium its chemically defined therapeutic acceptable compounds, mainly in the form of effervescent tablets, tablets, solutions, powders and the like, or as a source have served treated animal and mineral raw materials.

The drawback of the e.g. effervescent tablets, is the fact, that after a longer time they are refused by patients, because they can, in addition to others, induce shifts in the acid-base balance to a metabolic alkalosis, the transport of calcium into bloodstream is fast and calcium concentration may exceed the safe level to cause temporary hypercalcaemia, which is dangerous from the point of view of origin and development of atherosclerosis.

In the case, that improperly selected calcium compound as e.g. calcium chloride is used, the preparation can at a long-term administration induce metabolic acidosis connected with increasing washing up of calcium from the bony mass.

The drawback of biopreparations can be the presence of undesirable admixtures and non-standard content of biologically usable cations.

Another drawback is more time, raw materials and energy consuming manufacture.

Disclosure of the Invention

The substance of the pharmaceutical composition according to this invention is the dosaged formulation, containing as the active substance calcium in the amount of from 150 mg to 1500 mg, preferably from 200 mg to 600 mg, or the mixture of calcium with vitamin D, wherein vitamin D is in the amount of from 100 I.U to 1000 I.U, preferably from 400 I.U to 900 I.U, or the mixture of calcium and magnesium, wherein magnesium is in the amount of from 20 mg to 500 mg, preferably from 150 mg to 300 mg. Active substances containing calcium and magnesium are micronized so that at least 80 % of the particles are less than 75 micrometers in size.

The pharmaceutical composition according to the invention is in the form of instant powder, which after adding a liquid (water, milk, tea and the like), forms after a short mixing a pudding-like gelled suspension, tolerated during use by the patients, who use the preparations with above mentioned active substances for preventive or therapeutic reasons. The advantage is the precise dosage of the active substances.

The principle of the manufacture of above mentioned formulation is, that a balanced mixture of micronized active substances and adjuvants is prepared either by simple mixing or in the case of need of further machine treatment by granulating by means of water and ethanol mixture consisting of water in the range of 30 to 80 % by weight and ethanol in the range of 20 to 70 % by weight, preferably 60 % by weight of water and 40 % by weight of ethanol and by subsequent drying either in a chamber, in vacuo, by fluidization, or by microwave irradiation at the temperature of 30 to 60 °C, preferably 35 to 45 °C.

The obtained mixture appropriately adjusted in therapeutic doses into single dosage packages formed by a thermosealed combined foil preventing a passage of vapours

and gases, is chemically and physically stable and enables a simple manipulation in the preparation of suspension for therapeutic or preventive use by the patient.

The formulation according to this invention contains in addition to to the micronized active substances from the group of therapeutically acceptable salts of calcium, magnesium or from another sources such as treated eggshells, calcium shells of animals or inorganic minerals, and vitamins, additional adjuvants which are responsible for possibility of forming a gelled, pudding-like suspension tolerated by the patients. These are:

a) Pharmaceutically acceptable starch derivatives, preferably distarchphosphate in an amount of from 5 to 40 % by weight, preferably from 15 to 25 % by weight.

b) Mono and/or disaccharides, preferably saccharoses, in an amount of from 10 to 80 % by weight, preferably from 20 to 40 % by weight.

c) Substances of plant origin able to form with water xerogels, preferably carageenan in an amount of 0.1 to 1.0 % by weight, preferably 0.2 to 0.6 % by weight.

d) Pharmaceutically usable phosphoric acid salts, such as sodium hydrogenphosphate in an amount of from 0.05 to 0.45 % by weight, preferably from 0.1 to 0.35 % by weight and sodium phosphate in an amount of from 0.2 to 2.0 % by weight, preferably from 0.7 to 1.4 % by weight.

e) Corrigents of taste and odour of the pharmaceutical composition,

from the group of natural and naturally identical aromas in amounts from 0.1 to 5 % by weight, preferably from 0.5 to 1 % by weight,

from the group of artificial sweetening agents in amounts from 0.035 to 0.20 % by weight, preferably from 0.05 to 0.15 % by weight,

from the group of pharmaceutically usable organic acids, preferably citric acid in an amount of from 0.1 to 4 % by weight, preferably from 0.8 to 1,8 % by weight and salts thereof, preferably trisodiumcitrate in an amount from 0.05 to 2.0 % by weight, preferably from 0.1 to 0.5 % by weight,

cocoa powder in an amount of from 1 to 30 % by weight, preferably from 10 to 20 % by weight.

f) Substances correcting the appearance from the group of permitted natural and synthetic coloring agents in amounts from 0.001 to 0.005 % by weight, preferably from 0.002 to 0.004 % by weight.

g) Substances facilitating technological process, which prevent undesirable agglomeration of particles and antistatic affecting substances from the group of silicon oxides in amounts from 0.1 to 7.0 % by weight, lubricating agents from the group of magnesium, calcium and aluminium salts of higher fatty acids, preferably calcium stearate, or magnesium stearate in amounts of from 0.1 to 0.7 % by weight, preferably from 0.2 to 0.4 % by weight, or substances from the group of silicon organic compounds, preferably dimethylpolysiloxane in an amount of from 0.07 to 0.9 % by weight, preferably from 0.1 to 0.5 %.by weight.

h) Preserving agents, such as sorbic acid in an amount of from 0.01 to 0.04 % by weight, its salts, preferably sodium and potassium salt in amounts of from 0.01 to 0.05 % by weight, benzoic acid in an amount of from 0.006 to 0.02 % by weight, its salts, preferably sodium salt in an amount of from 0.01 to 0.03 % by weight, p-hydroxybenzoic acid esters in amounts of from 0.001 to 0.08 % by weight, preferably from 0.01 to 0.06 % by weight and salts thereof, preferably sodium and potassium salt in amounts of from 0.001 to 0.08 % by weight.

Examples

The following examples are intended to illustrate the invention without limiting its scope.

Example 1

a) pharmaceutical composition, containing in 1 dose:

Calcium carbonate	1.2474 g	41.58 %
Saccharose.....	1.1392 g	37.97 %

Starch derivative	0.4682 g	15.60 %
Carageenan	0.0122 g	0.41 %
Sodium hydrogenphosphate	0.0076 g	0.25 %
Sodium phosphate	0.0304 g	1.01 %
Citric acid	0.0300 g	1.00 %
Sodium citrate	0.0100 g	0.33 %
Orange aroma	0.0250 g	0.83 %
Maltodextrin	0.0210 g	0.70 %
Dimethylpolysiloxane	0.0090 g	0.30 %

b) *process for its preparation:*

Micronized calcium carbonate is agitated in a suitable apparatus along with saccharose and starch derivative, carageenan is added and agitation continued. In another mixing equipment sodium hydrogenphosphate, sodium phosphate, citric acid and sodium citrate, which are adjusted by sieving through a screen of the mesh size of 1.0 mm, are admixed. After homogeneity is reached, this mixture is added into the first mixture. Both mixtures are agitated along at least for 20 minutes and after homogenization is completed, dimethylpolysiloxane in the mixture with maltodextrin and powdered orange aroma are finally added. After reaching homogeneity confirmed by an analysis the obtained mixture is adjusted into one-dose sachets from combined foil, preferably PP/Al/PE, with one dose in the amount of 3.000 g. This way prepared 1 dose contains 500 mg of biologically usable calcium.

Example 2

a) pharmaceutical composition, containing in 1 dose:

Calcium carbonate	1.2474 g	41.58 %
Saccharose	0.8356 g	27.85 %
Starch derivative	0.3803 g	12.68 %
Carageenan	0.0088 g	0.30 %

Sodium hydrogenphosphate	0.0056 g	0.19 %
Sodium phosphate	0.0223 g	0.74 %
Cocoa powder	0.5000 g	16.66 %

b) process for its preparation:

Micronized calcium carbonate is agitated in a suitable apparatus along with the starch derivative, saccharose, carageenan, sodium hydrogenphosphate, sodium phosphate and cocoa powder pre-sieved through a screen of the mesh side of 1.25 mm, until homogeneous. The obtained mixture is moistened with a necessary amount of water and ethanol mixture until a desirable graininess is reached. The granulate is dried to moisture not exceeding 2,5 % by weight, its particles are adjusted to a size suitable for an adjustment and filled into one-dose sachets from combined foil PP/Al/PE with one dose in the amount of 3.000 g. This way prepared 1 dose contains 500 mg of biologically usable calcium.

Example 3

a) pharmaceutical composition, containing in 1 dose:

Calcium carbonate	1.2474 g	41.58 %
Saccharose	1.1992 g	39.97 %
Starch derivative	0.4855 g	16.18 %
Carageenan	0.0127 g	0.42 %
Sodium hydrogenphosphate	0.0080 g	0.27 %
Sodium phosphate	0.0320 g	1.06 %
Vanilla aroma	0.0150 g	0.50 %
Yellow synthetic colorant	0.0002 g	0.0066 %

b) process for its preparation:

Micronized calcium carbonate is agitated in a suitable pharmaceutical apparatus along with starch derivative, saccharose, carageenan, sodium hydrogenphosphate and sodium phosphate pre-sieved through a screen of the mesh side of 1.25 mm, until homogeneity is reached. This mixture is under agitation gradually moistened with the necessary amount of water and ethanol mixture and granulated. The granulate is dried by fluidization at the temperature of fed air 50 °C until residual moisture not exceeding 2.0 % by weight is reached. The dry mixture is transferred into a mixing device, desirable amounts of powdered vanilla aroma and colorant are added and the mixture is agitated until homogeneity is reached. By this process is the mixture prepared for adjustment into one-dose sachets from combined foil, with one dose in the amount of 3.000 g. This way prepared 1 dose contains 500 mg of biologically usable calcium.

Example 4

a) pharmaceutical composition, containing in 1 dose:

Calcium carbonate	1.2474 g	41.58 %
Saccharose	1.1334 g	37.78 %
Starch derivative	0.4664 g	15.55 %
Sodium hydrogenphosphate	0.0075 g	0.25 %
Sodium phosphate	0.0302 g	1.01 %
Carageenan	0.0120 g	0.40 %
Colecalciferol 100 000 I.U / g	0.0080 g	0.26 %
Citric acid	0.0300 g	1.00 %
Sodium citrate	0.0100 g	0.33 %
Yellow synhetic colorant	0.0001 g	0.003 %
Powdered peach aroma	0.0250 g	0.83 %
Maltodextrin	0.0210 g	0.70 %
Dimethylpolysiloxane	0.0090 g	0.30 %

b) process for its preparation

Micronized calcium carbonate is agitated in a suitable pharmaceutical apparatus along with saccharose and starch derivative, carageenan is added and agitation continued. After the accomplished homogenization sodium hydrogenphosphate, sodium phosphate, citric acid and sodium citrate pre-adjusted through a screen having the mesh side of 1.25 mm are stepwise added. In a special device for homogenization of small amounts colecalciferol is diluted with the mixture prepared before in the ratio of 1 : 50. Diluted colecalciferol is transferred into the mixture prepared before and admixed by intensive agitation until homogeneous. Yellow synthetic colorant, powdered peach aroma, maltodextrin and dimethylpolysiloxane are then stepwise added to the mixture. After homogenization is completed, the mixture is prepared to be adjusted into a combined three-layer foil PP/Al/PE in the doses of 3.000 g, what is one dose and this contains 500 mg of biologically usable calcium and 800 I.U. of vitamin D3.

Example 5

a) pharmaceutical composition, containing in 1 dose:

Calcium carbonate	1.2474 g	41.58 %
Saccharose	1.1856 g	39.52 %
Starch derivative	0.4816 g	16.05 %
Sodium hydrogenphosphate	0.0080 g	0.26 %
Sodium phosphate	0.030 g	1.00 %
Carageenan	0.0126 g	0.42 %
Colecalciferol 100 000 I.U	0.0080 g	0.26 %
Powdered coconut aroma	0.0250 g	0.83 %

b) process for its preparation:

Micronized calcium carbonate is agitated in a suitable pharmaceutical apparatus along with saccharose and starch derivative, carageenan is added and agitation continued. After accomplished homogenization, sodium hydrogenphosphate and sodium phosphate pre-adjusted through a screen having the mesh side of 1.25 mm are stepwise added. In a special device for homogenization of small amounts colecalciferol is diluted with the mixture prepared before in the ratio of 1 : 50. Diluted colecalciferol is transferred into the mixture prepared before and admixed by intensive agitation until homogeneity is reached. Then powdered coconut aroma is added to the mixture. After homogenization is completed, the mixture is prepared to be adjusted into a combined three-layer foil PP/Al/PE in the doses of 3.000 g, what is one dose and this contains 500 mg of biologically usable calcium and 800 I.U. of vitamin D3.

Example 6

a) pharmaceutical composition, containing in 1 dose:

Magnesiumhydroxidecarbonate	0.7880 g	26.26 %
Calcium carbonate	0.6237 g	20.79 %
Saccharose	0.9749 g	32.50 %
Starch derivative	0.4682 g	15.61 %
Carageenan	0.0122 g	0.40 %
Sodium hydrogenphosphate	0.0076 g	0.25 %
Sodium phosphate	0.0304 g	1.01 %
Citric acid	0.0300 g	1.00 %
Sodium citrate	0.0100 g	0.33 %
Powdered citric aroma	0.0250 g	0.83 %
Maltodextrin	0.0210 g	0.70 %
Dimethylpolysiloxane	0.0090 g	0.30 %

b) process for its preparation:

Micronized magnesium hydroxidecarbonate and calcium carbonate are admixed in a suitable apparatus with a half amounts of saccharose and starch

derivative. Carageenan is added, the mixture is perfectly commixed and the rests of saccharose and starch derivative are added. After accomplished homogenization previously homogenized mixture of sodium hydrogenphosphate, sodium phosphate, citric acid and sodium citrate with the adjusted size of particles through a screen of the mesh side of 1.0 mm is added to this mixture. When homogenization of these mixtures is completed, dimethylpolysiloxane, maltodextrin and powdered citric aroma are stepwise added. After reaching homogeneity confirmed by an analysis the mixture is adjusted into one-dose sachets from a combined three-layer foil, with doses in the amount of 3.000 g. This way prepared 1 dose contains 200 mg of biologically usable magnesium and 250 mg of biologically usable calcium

Clinical evaluation

Administration of calcium is essential part of every treatment or prevention of osteoporosis, wherein it is necessary to ensure a daily uptake of 400 to 800 I.U of vitamin D.

In the monocentric open controlled clinical study was proved similar bioavailability of calcium after single administration of the composition according to the invention in comparison with standard preparation in an effervescent tablet form, wherein distinctly higher calcaemia after 1 hour after administration of effervescent tablet was found out. Gradual increasing of calcaemia not exceeding the upper limit of the standard, is very desirable especially in elderly population where hypercalcaemia is connected with the risk of calcium deposition into atherosclerotic plates.

In the monocentric open uncontrolled tolerance clinical study with adult patients having osteoporosis or having insufficient intake of calcium in diet excellent tolerance and safety of the composition according to this invention was proved. The two month administration of followed up composition of the invention resulted in statistically significant increase of calcaemia in the whole group of 76 patients having osteopenia or osteoporosis proved by densitometry and having insufficient intake of calcium.

Characteristics of clinical studies with a composition of calcium according to the invention

Type of study	**Study of relative bioavailability (open, crossed, comparative)**
Number of followed up	12
Sex	Women
Characteristic	healthy volunteers
Age	18 - 30 years
Duration of follow up	single administration of medication
Medication	• followed up composition with calcium content according to the invention • reference standard preparation with the same content of calcium carbonate in the formulation of effervescent tbl., dose 1000 mg of elementary calcium was applicated
Parameters followed up	fS Ca and iPTH before administration, and 1, 2, 3, 4, 5 hours after administration
Results	• significant increase of fS Ca and decline of iPTH in all samplings • significant higher fS Ca in sampling one hour after administration of reference preparation • nonsignificant differences between the followed up composition and reference preparation in fS Ca and iPTH in other samplings • normal calcaemia in all samplings after use of followed up composition, • hypercalcaemia in 2 women after reference preparation

Type of study	**open, uncontrolled, clinical study of tolerance and safety**
Number of followed up	76
Sex	73 women, 3 men
Characteristic	patients with osteopenia or osteoporosis proved by densitometry and with insufficient calcium intake
Age	37 – 84 years
Medication	followed up composition in a dose 1 - 2 sachets daily (according to the calcium intake for given age and sex)
Duration of follow up	2 months
Parameters followed up	fS Ca, Ca/24 hours, anamnestic data about tolerance and satisfaction with composition
Results	• excellent or good tolerance in 99 % of patients, • low incidence and small relevancy of undesirable effects (they were reported by patients only in 19 % of rounds, only in 2 patients it was necessary to stop treatment because of undesirable effects), • good effectiveness (significant increase of mean calcaemia in the group after 2 months of treatment).

Industrial Applicability

The invention is useful in the pharmaceutical industry in the manufacture of therapeutic preparations for treatment and prevention of osteoporosis.

CLAIMS

1. A pharmaceutical composition with a content of calcium or mixture of calcium and vitamin D or mixture of calcium and magnesium **characterized in that** it contains as the active substance calcium in the amount of 150 to 1500 mg, preferably of 200 to 600 mg, or the mixture of calcium with vitamin D, wherein vitamin D is in the amount of 100 to 1000 I.U, preferably of 400 to 900 I.U, or the mixture of calcium and magnesium, which contains magnesium in the amount of 20 to 500 mg, preferably of 150 to 300 mg; wherein active substances calcium and magnesium are micronized so that at least 80 % of the particles are less than 75 micrometers in size.

2. The pharmaceutical composition according to claim 1 **characterized in that** it contains in addition to the micronized active substances, as adjuvants:
   - pharmaceutically acceptable starch derivatives, preferably distarchphosphate in an amount of from 5 to 40 % by weight, preferably from 15 to 25 % by weight;
   - mono and/or disaccharides, preferably saccharoses, in an amount of from 10 to 80 % by weight, preferably from 20 to 40 % by weight;
   - substances of plant origin able to form with water xerogels, preferably carageenan in an amount of 0.1 to 1.0 % by weight, preferably of 0.2 to 0.6 % by weight;
   - pharmaceutically usable phosphoric acid salts such as sodium hydrogenphosphate in an amount of from 0.05 to 0.45 % by weight, preferably from 0.1 to 0.35 % by weight and sodium phosphate in an amount of from 0.2 to 2.0 % by weight, preferably from 0.7 to 1.4 % by weight;
   - corrigents of taste and odour of the composition, from the group of natural and naturally identical aromas in an amount from 0.1 to 5 % by weight, preferably from 0.5 to 1 % by weight; from the group of artificial sweeetening agents in an amount from 0.035 to 0.20 % by weight, preferably from 0.05 to 0.15 % by weight; from the group of pharmaceutically usable organic acids, preferably citric acid, in an amount of from 0.1 to 4 % by weight, preferably from 0.8 to 1.8 % by

weight and salts thereof, preferably trisodiumcitrate in an amount of from 0.05 to 2.0 % by weight, preferably from 0.1 to 0.5 % by weight; cocoa powder in an amount of from 1 to 30 % by weight, preferably from 10 to 20 % by weight;

- and optionally substances correcting the appearance from the group of permitted natural and synthetic coloring agents in an amount of from 0.001 to 0.005 % by weight, preferably from 0.002 to 0.004 % by weight; substances facilitating technological process preventing undesirable agglomeration of particles and antistatic affecting substances from the group of silicon oxides in an amount from 0.1 to 7.0 % by weight, lubricating agents from the group of magnesium, calcium and aluminium salts of higher fatty acids, preferably calcium stearate or magnesium stearate in an amount of from 0.1 to 0.7 % by weight, preferably from 0.2 to 0.4 % by weight or substances from the group of silicon organic compounds, preferably dimethylpolysiloxane in an amount from 0.07 to 0.9 % by weight, preferably from 0.1 to 0.5 % by weight; preserving agents such as sorbic acid in an amount of from 0.01 to 0.04 % by weight, its salts, preferably sodium and potassium salt in an amount from 0.01 to 0.05 % by weight, benzoic acid in an amount of from 0.006 to 0.02 % by weight, its salts, preferably sodium salt in an amount of from 0.01 to 0.03 % by weight, p-hydroxybenzoic acid esters in amounts from 0.001 to 0.08 % by weight, preferably from 0.01 to 0.06 % by weight and salts thereof, preferably sodium and potassium salts in an amount of from 0.001 to 0.08 % by weight.

3. The pharmaceutical composition according to claims 1 and 2 **characterized in that** it is in the form of instant powder which after adding a liquid forms after a short mixing a pudding-like gelled suspension.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K33/06 A61K31/59 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 47122 A (SMTM GROUP LLC) 23 September 1999 (1999-09-23) abstract page 5, line 6 - line 12 page 6, line 18 -page 7, line 9 page 11, line 6 - line 9	1
X Y	US 5 587 399 A (ACOSTA PHYLLIS J B ET AL) 24 December 1996 (1996-12-24) tables 1,2	1 2,3
X Y	US 4 882 161 A (SCHEURER HEINRICH P ET AL) 21 November 1989 (1989-11-21) abstract column 1, line 49 - line 55 column 2, line 18 - line 37 column 3, line 15 -column 4, line 12	1 2,3

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
2 August 2001	13/08/2001

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 637 313 A (CHAU TOMMY L ET AL) 10 June 1997 (1997-06-10) abstract column 3, line 65 -column 4, line 62 column 5, line 39 table 2	1-3
Y	US 5 296 476 A (HENDERSON ESTHER G) 22 March 1994 (1994-03-22) example I	1-3
Y	US 4 650 669 A (ALEXANDER THOMAS A ET AL) 17 March 1987 (1987-03-17) column 4, line 13 - line 17 examples 6,7	1-3

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No
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